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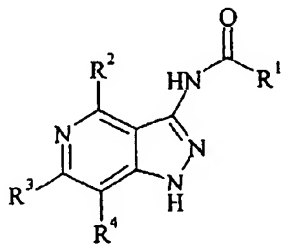
(54) Title: PYRAZOLOPYRIMIDINES DERIVATIVES



(I)

(57) Abstract: A compound of formula (I), or a salt thereof, or a solvate thereof, wherein R^1, R^2, R^3 and R^4 are as defined in the specification. These compound are indicated to be useful for the treatement and/or prophylaxis or conditions associated with a need for inhibition of GSK- 3,such a diabetes ,conditions associated with diabetes ,chronic neurodegenerative conditions including such as Alzheimer's disease , Parkinson's disease ,progressive supranuclear palsy ,subacute sclerosing panencephalitic parkinsonism , postencephatilic parkinsonism ,pugilistic encephalitics ,guam parkinsonism-dementia complex,Pick's disease,corticobasal degeneration,frontotemporal dementia, Huntingdon's disease, AIDS associated dementia , amyotrophic lateral sclerosis,multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders,promotion of functioal recovery post stroke,cerebral bleeding (for example ,due to solitary cerebral amyloid angiopathy), hair loss ,obesity, atherosclerotic cardiovasvular disease,hypertension , polycystic ovary synderome, syndrome X,ischaemia, traumatic brain injury ,cancer ,leukopenia ,Down syndrome ,Lewy body ,inflamation ,and immunodeficiency.

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Novel Compounds

This invention relates to novel compounds, in particular to novel pyrazolopyridine derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

GSK-3 is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al., Eur. J. Biochem.*, **(107)**, 519-527, (1980)). The α and β isoforms have a monomeric structure and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al., Biochemical Journal*, **(303)**, 21-26, (1994)) and these two isoforms show good homology between species (*e.g.* human and rabbit GSK-3α are 96% identical).

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage.

The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J., *Biochim. Biophys. Acta.*, **(39)**, 171-173, (1960), Parker P.J. *et al., Eur. J. Biochem.*, **(130)**, 227-234, (1983) and Cohen P., *Biochem. Soc. Trans.*, **(21)**, 555-567, (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A.K. and Pandey S.K., *Mol. and Cellular Biochem.*, **(182)**, 135-141, (1998)).

Chen *et al.* (*Diabetes*, **(43)**, 1234-1241, (1994)) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type II

diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3α activity and insulin action (Nikoulina *et al.*, *Diabetes*, **(49)**, 263-271, (2000)). Overexpression of GSK-3β and constitutively active GSK-3β(S9A, S9E) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman *et al.*, *PNAS*, **(93)**, 10228-10233, (1996)) and overexpression of GSK-3β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), resulted in an impairment of insulin action (Eldar-Finkelman and Krebs, *PNAS*, **(94)**, 9660-9664, (1997)). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin resistance and type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman *et al.*, *Diabetes*, **(48)**, 1662-1666, (1999)).

GSK-3 has been shown to phosphorylate other proteins *in vitro* including the eukaryotic initiation factor eIF-2B at $Serine^{540}$ (Welsh *et al.*, *FEBS Letts.*, **(421)**, 125-130, (1998)). This phosphorylation results in an inhibition of eIF-2B activity and leads to a reduction in this key regulatory step of translation. In disease states, such as diabetes, where there is elevated GSK-3 activity this could result in a reduction of translation and potentially contribute to the pathology of the disease.

Several aspects of GSK-3 functions and regulation in addition to modulation of glycogen synthase activity indicate that inhibitors of this enzyme may be effective in treatment of disorders of the central nervous system. GSK-3 activity is subject to inhibitory phosphorylation by PI 3 kinase-mediated or Wnt-1 class-mediated signals that can be mimicked by treatment with lithium, a low mM inhibitor of GSK-3 (Stambolic V., Ruel L. and Woodgett J.R., *Curr. Biol.*, **(6)**, 1664-8, (1996)).

GSK-3 inhibitors may be of value as neuroprotectants in treatment of acute stroke and other neurotraumatic injuries. Roles for PI 3-kinase signalling through PKB/akt to promote neuronal cell survival are well established, and GSK-3 is one of a number of PKB/akt substrates to be identified that can contribute to the inhibition of apoptosis via this pathway (Pap and Cooper, *J. Biol. Chem.*, **(273)**, 19929-19932, ((1998)). Evidence suggests that astrocytic glycogen can provide an alternative energy source to facilitate neuronal survival under conditions of glucose deprivation (for example, see Ransom B.R. and Fern R., *Glia*, **(21)**, 134-141, (1997) and references therein). Lithium is known to

protect cerebellar granule neurons from death (D'Mello *et al.*, *Exp. Cell Res.*, **(211)**, 332-338, (1994) and Volonte *et al.*, *Neurosci. Letts.*, **(172)**, 6-10, (1994)) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, *Neuroreport*, **(9)**, 2081-2084, (1998)). Wnt-induced axonal spreading and branching in neuronal culture models has been shown to correlate with GSK-3 inhibition (Lucas and Salinas, *Dev. Biol.*, **(192)**, 31-44, (1997)) suggesting additional value of GSK-3 inhibitors in promoting neuronal regeneration following neurotraumatic insult.

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early event in neurodegenerative conditions such as Alzheimer's disease (AD), and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules, and promote microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M., *J. Biol. Chem.*, **(272)**, 25326-32, (1997)). β-catenin is phosphorylated by GSK-3 as part of a tripartite complex with axin, resulting in β-catenin being targetted for degradation (Ikeda *et al.*, *J. EMBO.*, **(17)**, 1371-1384, (1998)). Inhibition of GSK-3 activity is a key mechanism by which cytosolic levels of catenin are stabilised and hence promote β-catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl, *Curr. Opin. Cell. Biol.*, **(11)**, 233, (1999)). Rapid onset AD mutations in presenilin-1 (PS-1) have been shown to decrease the cytosolic β-catenin pool in transgenic mice. Further evidence suggests that such a reduction in available β-catenin may increase neuronal sensitivity to amyloid mediated death through inhibition of β-catenin-LEF-1/TCF transcriptional regulation of neuroprotective genes (Zhang *et al.*, *Nature*, **(395)**, 698-702, (1998)). A likely mechanism is suggested by the finding that mutant PS-1 protein confers decreased inactivation of GSK-3 compared with normal PS-1 (Weihl C.C., Ghadge G.D., Kennedy S.G., Hay N., Miller R.J. and Roos R.P., *J. Neurosci.*, **(19)**, 5360-5369, (1999)).

International Patent Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is

lithium, but that there are serious drawbacks associated with this treatment. Whilst the precise mechanism of action of this drug for treatment of manic depression remains to be fully defined, current models suggest that inhibition of GSK-3 is a relevant target that contributes to the modulation of AP-1 DNA binding activity observed with this compound (see Manji *et al.*, *J. Clin. Psychiatry*, **(60)** (suppl 2), 27-39, (1999) for review).

GSK-3 inhibitors may also be of value in treatment of schizophrenia. Reduced levels of β-catenin have been reported in schizophrenic patients (Cotter D., Kerwin R., al-Sarraji S., Brion J.P., Chadwich A., Lovestone S., Anderton B., and Everall I., *Neuroreport*, **(9)**, 1379-1383, (1998)) and defects in pre-pulse inhibition to startle response have been observed in schizophrenic patients (Swerdlow *et al.*, *Arch. Gen. Psychiat.*, **(51)**, 139-154, (1994)). Mice lacking the adaptor protein dishevelled-1, an essential mediator of Wnt-induced inhibition of GSK-3, exhibit both a behavioural disorder and defects in pre-pulse inhibition to startle response (Lijam N., Paylor R., McDonald M.P., Crawley J.N., Deng C.X., Herrup K., Stevens K.E., Maccaferri G., McBain C.J., Sussman D.J., and Wynshaw-Boris A., *Cell*, **(90)**, 895-905, (1997)). Together, these findings implicate deregulation of GSK-3 activity as contributing to schizophrenia. Hence, small molecule inhibitors of GSK-3 catalytic activity may be effective in treatment of this mood disorder.

The finding that transient β-catenin stabilisation may play a role in hair development (Gat *et al.*, *Cell*, **(95)**, 605-614, (1998)) suggests that GSK-3 inhibitors could be used in the treatment of baldness.

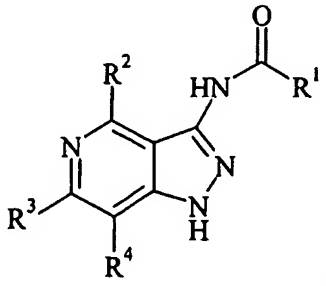
Studies on fibroblasts from the GSK-3β knockout mouse (Hoeflich K.P. *et al.*, *Nature*, **(406)**, 86-90, (2000)) support a role for this kinase in positively regulating the activity of NFkB. This transcription factor mediates cellular responses to a number of inflammatory stimuli. Therefore, pharmacologic inhibition of GSK-3 may be of use in treating inflammatory disorders through the negative regulation of NFkB activity.

The compounds of the present invention are pyrazolopyridine derivatives. Other pyrazolopyridine derivatives have been described previously for use in alternative medicinal applications. For example, International Patent Applications, Publication Numbers WO 97/23480 and WO 98/43962 describe various fused heterocyclic compounds, which may include pyrazolopyridines, which are useful as antagonists of the $\alpha_V\beta_3$-integrin and related cell surface adhesive protein receptors. Such compounds are

indicated to be useful in the treatment of conditions such as angiogenic disorders, inflammation, bone degradation, cancer metastasis, diabetic retinopathy, thrombosis, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis.

We have now discovered that a series of pyrazolo[4,3-c]pyridines are potent and selective inhibitors of GSK-3. These compounds are indicated to be useful for the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

Accordingly, in a first aspect, the present invention provides a compound of formula (I),



(I)

or a salt thereof, or a solvate thereof, wherein,

R^1 is alkyl, alkenyl, cycloC_{3-8} alkyl, cycloC_{3-8} alkenyl, di-alkylaminoalkyl, arylalkyl, arylalkenyl, heterocyclyl wherein the heterocyclyl group may be optionally substituted by one or more groups selected from alkyl, arylalkyl and alkoxyalkyl; heterocyclylalkyl

wherein the heterocyclyl may be optionally substituted by one or more groups selected from alkoxyalkyl, aryloxyalkyl, arylalkyl and alkyl; heteroaryllkyl wherein the heteroaryl group may be optionally substituted by one or more groups selected from alkyl; heteroaryl wherein the heteroaryl group may be optionally substituted by one or more groups selected from aryl and heteroaryl; aryl wherein the aryl group may be optionally substituted by heterocyclylalkyl and di-alkylaminoalkyl; or alkoxyalkyl wherein the alkoxy group may be optionally substituted by alkoxy;

R^2 is H;

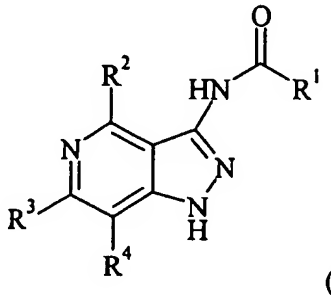
R^3 is aryl or heteroaryl wherein the aryl or heteroaryl group may be optionally substituted by one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, alkyl, alkenyl, C_{3-6} alkynyl, alkoxy, aryl, heteroaryl, and di-alkylamino; and

R^4 is H (hereinafter "the compounds of the invention").

Suitably, R^1 is alkyl, cycloC_{3-8} alkyl or heterocyclyl wherein the heterocyclyl group is further substituted by arylalkyl. Preferably, R^1 is iso-propyl, cyclo-propyl or N-benzylpyrrolidin-3-yl.

Suitably, R^3 is aryl or heteroaryl. Preferably, R^3 is phenyl or 2-furyl.

In a preferred aspect of the present invention there is provided a subset of compounds of formula (I), of formula (IA),



(IA)

or a salt thereof, or a solvate thereof, wherein,

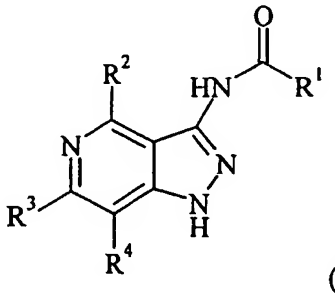
R^1 is alkyl, cycloC_{3-8} alkyl or heterocyclyl wherein the heterocyclyl group is further substituted by arylalkyl;

R^2 is H;

R^3 is aryl or heteroaryl; and

R^4 is H.

In a further preferred aspect of the present invention there is provided a subset of compounds of formula (I), of formula (IB),



(IB)

or a salt thereof, or a solvate thereof, wherein,

R^1 is iso-propyl, cyclo-propyl or N-benzylpyrrolidin-3-yl;

R^2 is H;

R^3 is phenyl or 2-furyl; and

R^4 is H.

Particularly preferred compounds of formula (I) which are of special interest as agents useful in the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3 are:

Cyclopropanecarboxylic acid (6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)-amide;

N-(6-Phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)isobutyramide;

N-(6-(Furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)isobutyramide;

(±)-1-Benzyl-N-(6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrrolidine-3-carboxamide hydrochloride; and

(±)-1-Benzyl-N-(6-(furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrrolidine-3-carboxamide hydrochloride.

Certain compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including geometric isomers and racemic modifications.

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl ("Pr^n"), *iso*-propyl ("Pr^i"), n-butyl ("Bu^n"), *sec*-butyl ("Bu^s"), *tert*-butyl ("Bu^t"), pentyl and hexyl. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical. Suitably such aryl groups are 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups, especially phenyl ("Ph"), biphenyl and naphthyl, particularly phenyl. Such aryl groups may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy and di-C_{1-6} alkylamino.

As used herein, the term "heteroaryl" as a group or part of a group refers to stable heterocyclic aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heteroaryl ring system may include carbocyclic rings and need include only one heteroaryl ring. Such heteroaryl groups include furyl, thienyl, pyridazinyl, pyridyl, quinolinyl, indolyl, thiazolyl, benzoxazolyl, and benzothiazolyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl, heteroaryl, and di-C_{1-6} alkylamino.

As used herein, the terms "heterocyclyl" and "heterocyclic" as a group or part of a group refer to stable heterocyclic non-aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heterocyclyl ring system may include carbocyclic rings and need include only one

heterocyclic ring. Such heterocyclyl groups include piperazinyl, pyrrolidinyl, piperidinyl and morpholinyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl, heteroaryl, arylC_{1-6} alkyl and di-C_{1-6} alkylamino.

Composite terms such as "alkoxyalkyl" and "arylalkyl" refer to substituents comprising two interlinked groups, with the group named latterly in the term being the linking group, so that "alkoxyalkyl" means -(alkyl)-(alkoxy) whilst "arylalkyl" means -(alkyl)-(aryl).

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, *inter alia*, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulfonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxyalkylamines such as

2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

For the avoidance of doubt when used herein the term "diabetes" includes diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

The term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

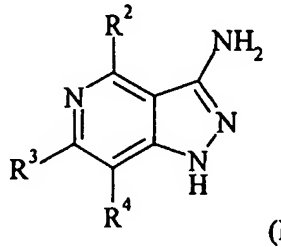
The term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

The term "conditions associated with diabetes mellitus itself" includes hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

The term "complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

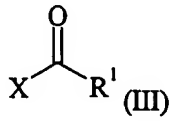
The term "neurotraumatic diseases" includes both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region, ischaemic stroke including acute stroke, particularly to the brain area, transient ischaemic attacks following coronary by-pass and cognitive decline following other transient ischaemic conditions.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I), or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3 and R^4 are as defined in relation to formula (I) with a compound of formula (III),



(III)

wherein R^1 is as defined in relation to formula (I) and X is a suitable leaving group and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

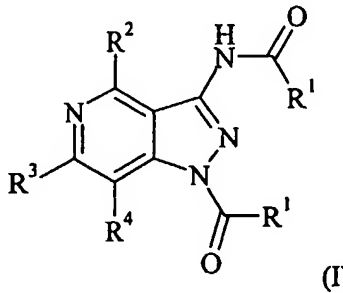
Suitably X is chloro. It will be appreciated that compounds of formula (III) may also include related carboxylic acid anhydrides.

The reaction between the compounds of formulae (II) and (III) is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is pyridine. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 0.5 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such

as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, to a compound of formula (II) in dry pyridine under an inert atmosphere, such as argon, is added a compound of formula (III). The reaction mixture is stirred at ambient temperature for 2 hours. The mixture is evaporated to dryness *in vacuo*, triturated with sodium hydrogen carbonate solution, filtered and dried to afford the desired compound of formula (I).

It will be appreciated that treatment of a compound of formula (II) with a compound of formula (III), according to the above-mentioned process, may lead to the formation of a *bis*-acylated intermediate species of formula (IV),



(IV)

wherein R^2, $R^3$and R^4 are as defined in relation to formula (I).

In a further aspect of the present invention, there is provided a process for the preparation of a compound of formula (I), or a salt and/or solvate thereof, which process comprises reacting a compound of formula (IV) with a nucleophile and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

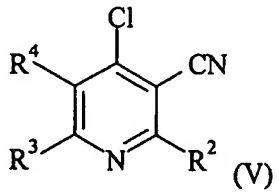
(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (IV) and a nucleophile is carried out optionally in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitably the reaction is performed using the nucleophile as a solvent. A suitable nucleophile is an amine, such as a primary or secondary amine, for example, piperidine. Suitable reaction temperatures include those in the range of 20°C to 100°C

and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a compound of formula (IV) is dissolved in a suitable nucleophile, such as piperidine, and stirred for 1 hour. The resulting mixture is concentrated *in vacuo* and the residue is purified by silica chromatography using one or more suitable solvents, such as a mixture of methanol and dicholoromethane, to afford the desired compound of formula (I).

Compounds of formula (II) may be prepared by reaction of a compound of formula (V),



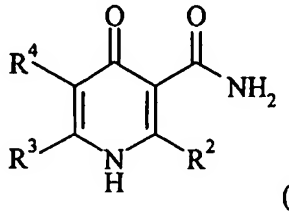
(V)

wherein, R^2, R^3 and R^4 are as defined in relation to formula (I), with hydrazine or a hydrate thereof.

The reaction between the compound of formula (V) and hydrazine or a hydrate thereof, is carried out in a suitable solvent at a suitable temperature, generally an elevated temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is pyridine. Suitable reaction temperatures include those in the range of 60 °C to 220 °C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-72 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the product isolated by filtration, and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, to a solution of a compound of formula (V) in ethanol is added hydrazine hydrate. The reaction mixture is heated under reflux, with stirring, for 16 hours. The resulting mixture is reduced *in vacuo* and the residue triturated with water and filtered to afford the desired compound of formula (II).

Compounds of formula (V) may be prepared by reaction of a compound of formula (VI),



(VI)

wherein, R^2, R^3 and R^4 are as defined in relation to formula (I), with a suitable halogenation/dehydration agent.

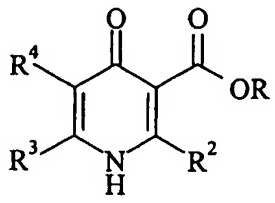
The reaction between the compound of formula (VI) and a halogenation/dehydration agent is carried out in a suitable solvent at a suitable temperature, generally an elevated temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitably, the halogenation/dehydration agent is used as a solvent. A suitable halogenation/dehydration agent is phosphoryl chloride. Suitable reaction temperatures include those in the range of 60 °C to 220 °C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-12 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the product isolated by filtration, and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, a solution comprising a compound of formula (VI) and phosphoryl chloride is heated under reflux for 4 hours. The resulting solution is evaporated to dryness *in vacuo* and the residue is treated with water, basified with sodium carbonate, and extracted with dichloromethane. The extract is dried with magnesium sulfate and evaporated *in vacuo*. The resulting solid is purified by silica gel

chromatography using one or more suitable solvents, such as a mixture of ethyl acetate and hexane, to afford the desired compound of formula (V).

It will be appreciated that as used herein the term "halogenation/dehydration agent" means any agent or mixture of agents capable of effecting both halogenation and dehydration.

Compounds of formula (VI) may be prepared by reaction of a compound of formula (VII),



(VII)

wherein, R^2, R^3 and R^4 are as defined in relation to formula (I) and where R is an alkyl or aryl group, with ammonia.

The reaction between the compound of formula (VII) and ammonia is carried out in a suitable solvent at a suitable temperature, generally an elevated temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is ethanol. Suitable reaction temperatures include those in the range of 60 °C to 220 °C and, as appropriate, the reflux temperature of the solvent. Suitably, the reaction is performed in a sealed vessel. Suitable reaction times are those in the range 1-12 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the product isolated by filtration, and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, a solution comprising a compound of formula (VII), ethanol and aqueous ammonia is heated at 100 °C for 3 hours in a pressure vessel. The resulting solution is concentrated *in vacuo* and the residue triturated with dichloromethane and filtered to afford the desired compound of formula (VI).

Compounds of formula (VII) may be prepared in accordance with procedures described by Kiyama *et al.* (*Chem. Pharm. Bull*, **(43)**, 450, (1995)).

Compounds of formula (II), (IV), (V) and (VI) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formulae (I), (II), (VI) and (VII) may exist as tautomers. The present invention encompasses all tautomeric forms of the compounds of (I), (II), (VI) and (VII).

As stated above, the compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

The invention therefore provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an inhibitor of GSK-3.

Accordingly, the present invention also provides a method for the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The present invention further provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes,

chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

In a further aspect of this invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

Preferably, the compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, are administered as pharmaceutically acceptable compositions.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The active compounds are usually administered as the sole medicament agent but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated.

The said combination comprises co-administration of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and the additional medicament agent.

Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a pharmaceutically acceptable salto or solvate thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and the additional medicament agent.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar,

maize starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a

surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) or the above-mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above-mentioned reference texts.

GSK-3 Assay

GSK-3 assays used to test the compounds of the invention include the following protocol which is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot- KYRRAAVPPSPSLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads (Amersham Technology), where the signal from the ^{33}P is amplified via the scintillant contained in the beads.

Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [^{33}P]-ATP. After incubation at room temperature, the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). IC_{50} values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show IC_{50} values in the range of 1 to 500 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Descriptions and Example illustrate the invention, but do not limit it in any way.

Synthetic Method A

Example 1

Cyclopropanecarboxylic acid (6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)-amide

6-Phenyl-1H-pyrazolo[4,3-c]pyridin-3-ylamine (0.080 g, 0.38 mmol) was stirred under argon in dry pyridine with cyclopropanecarbonyl chloride (0.076 mL, 0.84 mmol) for 2 hours. The mixture was then evaporated to dryness, triturated with sodium hydrogen carbonate solution, filtered, and dried. This gave a solid including the 1,3-diacylated material, cyclopropane carboxylic acid [1-(1-cyclopropylmethanoyl)-6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl]-amide, MS (ES +ve): $[M+H]^+$ at m/z 347. ($C_{20}H_{18}N_4O_2$ requires $[M+H]^+$ at m/z 347).

This material was dissolved in piperidine (2 mL), and stirred for 1 hour. Solvent was evaporated *in vacuo*, and the residue purified by chromatography on silica gel, eluting with 2%, 5% and 10% methanol in dichloromethane. Pure fractions were combined and evaporated to give the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 279. ($C_{16}H_{14}N_4O$ requires $[M+H]^+$ at m/z 279).

^1H NMR δ (DMSO-d6): 0.85 (4H, m), 1.98 (1H, m), 7.4-7.55 (3H, m), 7.84 (1H, s), 8.14 (2H, d), 9.31 (1H, s), 11.07 (1H, s), 13.02 (1H, s).

The starting material for Example 1 may be prepared by the methods of Descriptions 1 and 2.

Description 1

4-Chloro-5-cyano-2-phenylpyridine

Ethyl 4-oxo-6-phenyl-1,4-dihydropyridine-3-carboxylate (Chem. Pharm. Bull. 1995, 43(3), 450) (1.30 g, 5.3 mmol) was dissolved in ethanol (10 mL) and aqueous ammonia (d 0.88, 30 mL), sealed in a Berghof pressure apparatus, and stirred at 100°C for 3 hours. The solvents were then evaporated *in vacuo*, and the residue was triturated with dichloromethane. Filtration gave the intermediate amide as a solid. MS (ES +ve): $[M+H]^+$ at m/z 215. ($C_{12}H_{10}N_4O$ requires $[M+H]^+$ at m/z 215).

This material was stirred at reflux in phosphoryl chloride (10 mL) for 4 hours, cooled, and evaporated to dryness. The residue was treated with water, basified with solid sodium carbonate, and then extracted with dichloromethane. The extract was dried (magnesium sulfate) and evaporated to give a buff solid. Purification by chromatography on silica gel, eluting with 10% ethyl acetate in hexane, gave the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 215/217. ($C_{12}H_7ClN_2$ requires $[M+H]^+$ at m/z 215/217).

^1H NMR δ ($CDCl_3$): 7.50-7.55 (3H, m), 7.89 (1H, s), 8.04 (2H, m), 8.88 (1H, s).

Description 2

6-Phenyl-1H-pyrazolo[4,3-c]pyridin-3-ylamine

4-Chloro-5-cyano-2-phenylpyridine (0.10 g, 0.47 mmol) was stirred at reflux in ethanol (10 mL) with hydrazine hydrate (0.11 mL, 2.27 mmol) for 16 hours. Solvents were removed *in vacuo*, and the residue was triturated with water and filtered, giving the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 211. ($C_{12}H_{10}N_4$ requires $[M+H]^+$ at m/z 211).

^1H NMR δ (DMSO-d6): 5.77 (2H, s), 7.3-7.5 (3H, m), 7.64 (1H, s), 8.05 (2H, d), 9.01 (1H, s), 11.88 (1H, s).

Synthetic Method A

Example 2

N-(6-Phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)isobutyramide

6-Phenyl-1H-pyrazolo[4,3-c]pyridin-3-ylamine (0.092 g, 0.44 mmol) was stirred under argon in dry pyridine (3 mL) with isobutyryl chloride (0.11 mL, 1.05 mmol) for 2h. The mixture was then evaporated to dryness, triturated with sodium hydrogen carbonate solution, filtered, and dried. This gave a solid including the 1,3-diacylated material, N-[1-(2-methylpropanoyl)-6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl]isobutyramide.

MS (ES +ve): $[M+H]^+$ at m/z 351. ($C_{20}H_{22}N_4O_2$ requires $[M+H]^+$ at m/z 351).

^1H NMR δ ($CDCl_3$): 1.36 (12H, m), 2.73 (1H, m), 3.76 (1H, m), 7.4-7.55 (3H, m), 7.95 (1H, s), 8.13 (2H, d), 8.73 (1H, s), 9.64 (1H, s).

This material was dissolved in piperidine (5 mL), and stirred for 16 hours. Solvent was evaporated *in vacuo*, and the residue was triturated with water. The product was collected and dried to give the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 281. ($C_{16}H_{16}N_4O$ requires $[M+H]^+$ at m/z 281).
^1H NMR δ (DMSO-d_6): 1.18 (6H, d), 2.78 (1H, m), 7.42 (1H, t), 7.49 (2H, t), 7.85 (1H, s), 8.15 (2H, d), 9.32 (1H, s), 10.70 (1H, s), 13.04 (1H, s).

Synthetic Method A

Example 4

N-(6-(Furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)isobutyramide

6-(Furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-ylamine (0.100 g, 0.50 mmol) was stirred under argon in dry pyridine (5 mL) with isobutyryl chloride (0.13 mL, 1.24 mmol) for 2 hours. The mixture was then evaporated to dryness, triturated with sodium hydrogen carbonate solution, filtered, and dried. This gave a solid including the 1,3-diacylated material, N-[1-(2-methylpropanoyl)-6-(furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl]isobutyramide, MS (ES +ve): $[M+H]^+$ at m/z 341. ($C_{18}H_{20}N_4O_3$ requires $[M+H]^+$ at m/z 341), ^1H NMR δ ($CDCl_3$): 1.34 (12H, m), 2.72 (1H, m), 3.74 (1H, m), 6.55 (1H, dd), 7.19 (1H, d), 7.56 (1H, d), 7.94 (1H, s), 8.63 (1H, s), 9.55 (1H, s).
This material was dissolved in piperidine (4 mL), and stirred at room temperature for 16 hours. Solvent was evaporated *in vacuo*, and the residue was triturated with water. The product was collected and dried to give the title compound as a solid.
MS (ES +ve): $[M+H]^+$ at m/z 271. ($C_{14}H_{14}N_4O_2$ requires $[M+H]^+$ at m/z 271).
^1H NMR δ (DMSO-d_6): 1.17 (6H, d), 2.77 (1H, m), 6.65 (1H, m), 7.09 (1H, d), 7.60 (1H, s), 7.82 (1H, s), 9.24 (1H, s), 10.72 (1H, s), 13.0 (1H, br s).

The starting material for Example 4 may be prepared by the methods of Descriptions 3 and 4.

Description 3

4-Chloro-5-cyano-2-(furan-2-yl)pyridine

Methyl 4-hydroxy-6-(furan-2-yl)pyridine-3-carboxylate (by the method of Chem. Pharm. Bull. 1995, *43(3)*, 450) (3.41 g, 15.5 mmol) was dissolved in ethanol (30 mL) and aqueous ammonia (d 0.88, 60 mL), sealed in a Berghof pressure apparatus, and stirred at 100°C for 3 hours. The solvents were then evaporated *in vacuo*, and the residue was

triturated with dichloromethane. Filtration gave the intermediate hydroxyamide as an off-white solid.

This material was stirred at reflux in phosphoryl chloride (30 mL) for 4 hours, cooled, and evaporated to dryness. The residue was treated with water, basified with solid sodium carbonate, and then extracted with dichloromethane. The extract was dried (magnesium sulphate) evaporated to dryness and then purified by chromatography on silica gel, eluting with 10% ethyl acetate in hexane to give the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 205/207. ($C_{10}H_5ClN_2O$ requires $[M+H]^+$ at m/z 205/207).

^1H NMR δ ($CDCl_3$): 6.61 (1H, dd), 7.29 (1H, dd), 7.63 (1H, s), 7.81 (1H, s), 8.76 (1H, s).

Description 4

6-(Furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-ylamine

4-Chloro-5-cyano-2-(furan-2-yl)pyridine (2.02 g, 9.9 mmol) was stirred at reflux in ethanol (100 mL) with hydrazine hydrate (2.4 mL, 49.5 mmol) for 12 hours. Solvents were removed *in vacuo*, and the residue was triturated with water and filtered. The solid so obtained was then stirred at reflux in ethanol (100 mL) for 4 days, and evaporated to dryness, giving the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 201. ($C_{10}H_8N_4O$ requires $[M+H]^+$ at m/z 201).

^1H NMR δ (DMSO-d_6): 5.77 (2H, s), 6.62 (1H, d), 7.04 (1H, d), 7.42 (1H, s), 7.78 (1H, s), 8.93 (1H, s), 11.86 (1H, s).

Synthetic Method B

Example 3

(±)-1-Benzyl-N-(6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrrolidine-3-carboxamide hydrochloride

(±)-N-Benzylpyrrolidine-3-carboxylic acid hydrochloride (0.386 g, 1.60 mmol) was stirred in thionyl chloride (10 mL) for 2 hours, and evaporated to dryness. Residual thionyl chloride was removed by addition and evaporation of dry toluene. To the gummy residue was added 6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-ylamine (0.084 g, 0.40 mmol) and dry pyridine (10 mL). The mixture was stirred at 115°C for 16hours, evaporated to dryness, taken up in dichloromethane, and washed with sodium hydrogen carbonate solution. Purification by chromatography on silica gel, eluting successively with 0%,

2.5%, 5% and 10% methanol in dichloromethane gave the free base of the title compound as a solid. This was suspended in dichloromethane and treated with excess 1M hydrogen chloride in diethyl ether. The supernatant liquid was decanted, and the solid was washed once with ether, and dried, giving the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 398. ($C_{24}H_{23}N_5O.HCl$ requires $[M+H]^+$ at m/z 398).

^1H NMR δ (DMSO-d_6): 2.1-2.6 (2H, m), 3.25 (1H, m), 3.5-3.9 (4H, m), 4.5-4.6 (2H, m), 7.47 (3H, m), 7.6-7.7 (5H, m), 8.05-8.15 (3H, m), 9.64 (1H, s), 10.80 and 11.17 (1H, 2 x br s), 11.64 (1H, br s), 14.06 (1H, br s).

Synthetic Method B

Example 5

(±)-1-Benzyl-N-(6-(furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrrolidine-3-carboxamide hydrochloride

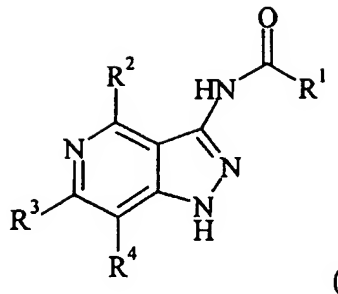
(±)-N-Benzylpyrrolidine-3-carboxylic acid hydrochloride (0.48 g, 1.99 mmol) was stirred in thionyl chloride (10 mL) for 2 hours, and evaporated to dryness. Residual thionyl chloride was removed by addition and evaporation of dry toluene. To the gummy residue was added 6-(furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-ylamine (0.100 g, 0.50 mmol) and dry pyridine (10 mL). The mixture was stirred at 115°C for 16 hours, evaporated to dryness, taken up in dichloromethane, and washed with sodium hydrogen carbonate solution. Purification by chromatography on silica gel, eluting successively with 0%, 2.5%, 5% and 10% methanol in dichloromethane gave the free base of the title compound as a light brown solid. This was suspended in dichloromethane and treated with excess 1M hydrogen chloride in ether. The supernatant liquid was decanted, and the solid was washed once with ether, and dried, giving the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 388. ($C_{22}H_{21}N_5O_2.HCl$ requires $[M+H]^+$ at m/z 388).

^1H NMR δ (DMSO-d_6): 2.1-2.6 (2H, m), 3.25 (1H, m), 3.4-3.7 (4H, m), 4.5-4.6 (2H, m), 6.80 (1H, s), 7.47 (3H, m), 7.65 (3H, m), 7.95 (1H, s), 8.02 (1H, s), 9.54 (1H, s), 10.86 and 11.32 (1H, 2 x br s), 11.61 (1H, br s), 14.03 (1H, br s).

Claims

1. A compound of formula (I),



(I)

or a salt thereof, or a solvate thereof, wherein,

R^1 is alkyl, alkenyl, cycloC_{3-8} alkyl, cycloC_{3-8} alkenyl, di-alkylaminoalkyl, arylalkyl, arylalkenyl, heterocyclyl wherein the heterocyclyl group may be optionally substituted by one or more groups selected from alkyl, arylalkyl and alkoxyalkyl; heterocyclylalkyl wherein the heterocyclyl may be optionally substituted by one or more groups selected from alkoxyalkyl, aryloxyalkyl, arylalkyl and alkyl; heteroaryllkyl wherein the heteroaryl group may be optionally substituted by one or more groups selected from alkyl; heteroaryl wherein the heteroaryl group may be optionally substituted by one or more groups selected from aryl and heteroaryl; aryl wherein the aryl group may be optionally substituted by heterocyclylalkyl and di-alkylaminoalkyl; or alkoxyalkyl wherein the alkoxy group may be optionally substituted by alkoxy;

R^2 is H;

R^3 is aryl or heteroaryl wherein the aryl or heteroaryl group may be optionally substituted by one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, alkyl, alkenyl, C_{3-6} alkynyl, alkoxy, aryl, heteroaryl, and di-alkylamino; and

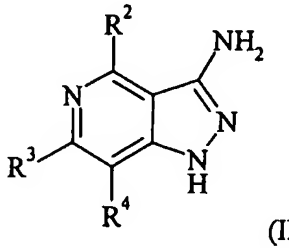
R^4 is H.

2. A compound of formula (I), as claimed in claim 1, wherein R^1 is iso-propyl, cyclopropyl or N-benzylpyrrolidin-3-yl.

3. A compound of formula (I), as claimed in claim 1 or claim 2, wherein R^3 is phenyl or 2-furyl.

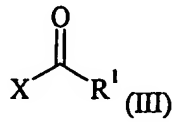
4. A compound of formula (I), as claimed, in claim 1, selected from:
Cyclopropanecarboxylic acid (6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)-amide;
N-(6-Phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)isobutyramide;
N-(6-(Furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)isobutyramide;
(±)-1-Benzyl-N-(6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrrolidine-3-carboxamide hydrochloride; and
(±)-1-Benzyl-N-(6-(furan-2-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrrolidine-3-carboxamide hydrochloride.

5. A process for the preparation of a compound of formula (I), or a salt and/or solvate thereof, as claimed in claim 1, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3 and R^4 are as defined in relation to formula (I) with a compound of formula (III),



(III)

wherein R^1 is as defined in relation to formula (I) and X is a suitable leaving group and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

6. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier.

7. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use as an active therapeutic substance.

8. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3

INTERNATIONAL SEARCH REPORT

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PCT/EP 03/03198

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P25/00 A61P9/00 A61P29/00
A61P37/00 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 81345 A (WELFIDE) 1 November 2001 (2001-11-01) abstract	1,6-8
P,A	WO 02 50073 A (SMITHKLINE BEECHAM) 27 June 2002 (2002-06-27) claims 1,11,12	1,6-8
P,A	WO 02 24694 A (SMITHKLINE BEECHAM) 28 March 2002 (2002-03-28) claims 1,14	1,6-8
P,A	WO 02 088078 A (VERTEX PHARMA) 7 November 2002 (2002-11-07) page 55, line 9 - line 33; claims 1,16	1,6-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	30/06/2003

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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		EP 1319001 A1	18-06-2003
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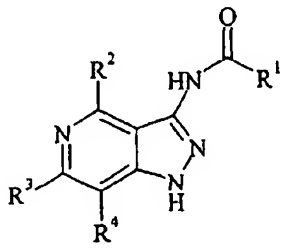
Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLOPYRIMIDINES DERIVATIVES



(I)

(57) Abstract: A compound of formula (I), or a salt thereof, or a solvate thereof, wherein, R^1, R^2, R^3 and R^4 are as defined in the specification. These compound are indicated to be useful for the treatement and/or prophylaxis or conditions associated with a need for inhibition of GSK- 3,such a diabetes ,conditions associated with diabetes ,chronic neurodegenerative conditions including such as Alzheimer's disease , Parkinson's disease ,progressive supranuclear palsy ,subacute sclerosing panencephalitic parkinsonism , postencephatilic parkinsonism ,pugilistic encephalitics ,guam parkinsonism-dementia complex,Pick's disease,corticobasal degeneration,frontotemporal dementia, Huntingdon's disease, AIDS associated dementia , amyotrophic lateral sclerosis,multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders,promotion of functioal recovery post stroke,cerebral bleeding (for example ,due to solitary cerebral amyloid angiopathy), hair loss ,obesity, atherosclerotic cardiovasvular disease,hypertension , polycystic ovary synderome, syndrome X,ischaemia, traumatic brain injury ,cancer ,leukopenia ,Down syndrome ,Lewy body ,inflamation ,and immunodeficiency.

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